mass difference between any pair of peaks in these four spectra must correspond to the total mass associated with the nucleotides in that portion of the sequence. This provides a significant redundancy in the results, which may be useful for analysis other than that involving the simple ordering of the peaks, a feature which is not available in electrophoresis. If a peak is very weak and is missed, or if two peaks are insufficiently resolved, a base may be missed by simple ordering. The mass difference observed between the next pair of adjacent peaks will thus show the error and allow correction. The computer may thus interpret the spectra and directly produce the sequence of bases in the DNA fragment. If there are any regions of the spectrum where the results may be consider ambiguous or unreliable, e.g., because the observed mass differences are inconsistent, those regions may be flagged so that the operator may perform either manual study or further automated analysis on those regions.

According to the technique of this invention a MALDI mass spectrometer is used rather than electrophoresis separation for DNA sequencing. Until recently, the MALDI technique was limited to single-stranded DNA fragments up to about 50 bases in length, but the range has now been extended to fragments as large as 500 bases in length.

Conventional large-scale sequencing is currently being done at a rate approaching 1 Mb per year of finished sequence. The cost of sequencing is in the vicinity of one U.S. dollar per base. A rate of 500 Mb per year is required for the Human Genome Project. A price of 20 cents per finished base is commensurate with the budget and goals of this project.

At the present stage of development, MALDI analysis of DNA fragments can be done readily on mixtures containing components less than 50 bases in length. Recent work suggests that this fragment length can be extended, perhaps as much as one order of magnitude to fragments 500 bases in length. Large scale sequencing would proceed much more rapidly by this technique if the fragments analyzed could be extended significantly. A reasonable goal is to be able to accurately analyze mixtures containing oligimers up to 300 bases in length. The resolution and sensitivity of presently available instruments is satisfactory. Even with the limitations imposed by the short segments, the MALDI technique with application of the present invention could be competitive with conventional approaches.

The present invention can readily handle at least 4 samples per minute, which corresponds with 50 base fragments to 50 bases of raw data per minute, since 4 separate samples are required to sequence each segment. A single instrument can run at least 1200 minutes per day to provide 60,000 bases per day of raw sequence. This is about 22 Mb/year from a single instrument. This is raw data, however, and the piecing together of fragments from short sequence generated data is likely to require considerable redundancy. Nevertheless, a single instrument, even with the limitations imposed by short segments, can surpass the total output of present conventional sequencing. The price for this instrument is about $200,000, and it should have a useful life of at least 5 years. Total cost for operating and maintaining the instrument (including amortization) should be less than $100,000/year. If the instrument produces 2 Mb of finished sequence/year, this corresponds to 5 cents/base. 250 such instruments would be required to provide sequences at the rate required by the Human Genome Project. If the length of the fragments analyzed can be extended, the speed will increase and the cost will rapidly decrease since less redundancy will be required. If the fragment length was increased to 300 bases, the raw data rate increases proportionally to about 120 Mb/year. The ratio of this raw rate to finished data rate should improve dramatically and may approach 50 Mb/year for a single instrument. In this case, ten instruments could provide the rate required by the Human Genome Project at a cost of 0.2 cent per base. Although this rate would not include the cost of sample preparation and data analysis, the rate and cost of raw sequence determination would no longer be the limiting feature.

It should be understood that this invention has been disclosed so that one skilled in the art may appreciate its features and advantages, and that a detailed description of specific components and the spacing and size of the components is not necessary to obtain that understanding. Many of the individual components of the mass spectrometer are conventional in the industry, and accordingly are only schematically depicted. The foregoing disclosure and description of the invention are thus explanatory, and various details in the construction of the equipment are not included. Alternative embodiments and operating techniques will become apparent to those skilled in the art in view of this disclosure, and such modifications should be considered within the scope of the invention, which is defined by the following claims.

What is claimed is:

1. A system for analyzing a plurality of samples, comprising:

a plurality of portable sample supports each having a sample receiving surface thereon for accommodating a plurality of samples each at a fixed location on each sample support;

identification means for identifying each sample location of each of the plurality of samples on each of the plurality of sample supports;

a mass spectrometer for analyzing each of the plurality of samples on each sample support, the mass spectrometer having a sample receiving chamber therein for receiving each sample support;

a laser source for striking each sample on each sample support while within the receiving chamber with a laser pulse to desorb and ionize sample molecules;

support transfer mechanism for automatically inputting and outputting each of the sample supports from the sample receiving chamber of the mass spectrometer;

a powered mechanism movable in both an x direction and a y direction perpendicular to the x direction within the sample receiving chamber for supporting a respective sample support thereon;

a vacuum lock chamber connected to the sample receiving chamber of the mass spectrometer for receiving the sample supports and for maintaining one or more of the sample supports within a vacuum controlled environment while the plurality of samples on another of the sample supports are struck by laser pulses; and

computer means for recording test data from the mass spectrometer for each of the plurality of samples on the sample supports as a function of the identification means.

2. The system as defined in claim 1, further comprising;

a sample loading mechanism for positioning each of a plurality of liquid samples on the sample receiving surface of each of the plurality of sample supports; and

a curing chamber for drying each of the plurality of liquid samples on each of the sample supports to form a plurality of solid samples each positioned on a respective sample support.

3. The system as defined in claim 2, further comprising:

sample support positioning means for positioning each liquid sample on the sample receiving surface of a respective sample support.

4. The system as defined in claim 2, further comprising:

a sample preparation mechanism for automatically preparing each of the plurality of liquid samples for a deposit on a respective sample support.

5. The system as defined in claim 4, wherein the sample preparation mechanism includes a first plurality of containers for receiving respective dilutions and a second plurality of containers for receiving respective matrixes for preparing each of the plurality of liquid samples each containing a selected dilution.

6. The system as defined in claim 5, further comprising:

valve means responsive to the computer means for automatically controlling the flow of fluids from the first and second plurality of containers.

7. The system as defined in claim 1, further comprising:

a pump responsive to the computer means for pumping liquid samples to a respective one of the sample supports.

8. The system as defined in claim 7, further comprising:

a drying chamber for drying liquid samples on each of the sample supports to form dried samples.

9. The system as defined in claim 8, further comprising:

vacuum means for controlling a vacuum within the drying chamber in response to the computer means.

10. The system as defined in claim 1, wherein each of the plurality of portable sample supports comprises an electrically conductive sample plate having a plurality of predetermined sample positions on the sample receiving surface.

11. The system as defined in claim 10, wherein each of the plurality of predetermined positions on the sample plate includes a well for receiving a respective sample.

12. The system as defined in claim 11, wherein each of the plurality of wells on the sample plate are arranged in one of a plurality of rows and in one of a plurality of columns.

13. The system as defined in claim 1, wherein:

the identification means includes a marking on each sample support for identifying each of the plurality of samples on the sample receiving surface.

14. The system as defined in claim 1, wherein a sample support includes a magnetic handle for cooperating with the support transfer mechanism to position the sample support.

15. The system as defined in claim 1, wherein each of the plurality of sample supports includes a sample holder and a plurality of pins each removably positionable with respect to the sample holder, each of the plurality of pins having a sample receiving surface thereon for receiving a respective one of the plurality of samples.

16. The system as defined in claim 1, wherein each of the plurality of sample supports has one or more locating members for precisely positioning the sample support.

17. The system as defined in claim 1, wherein each of the sample supports comprises in excess of 80 determined sample positions on the sample receiving surface.

18. The system as defined in claim 1, further comprising:

sample support identification means for identifying each of the plurality of sample supports and for inputting sample support identification information to the computer means.

19. The system as defined in claim 1, further comprising:

a sample storage chamber for storing one or more of the plurality of sample supports; and

a powered transporter for transporting each of the plurality of sample supports from the sample storage chamber to the vacuum lock chamber.

20. The system as defined in claim 19, wherein the powered transporter is automatically responsive to the computer means.

21. The system as defined in claim 19, further comprising:

a transport cassette for supporting a plurality of sample supports each in a preselected position within the sample storage chamber.

22. The system as defined in claim 21, further comprising:

a transport drive mechanism for selectively positioning the transport cassette within the sample storage chamber.

23. The system as defined in claim 22, wherein the transport drive mechanism is powered in response to the computer means.

24. The system as defined in claim 23, wherein the transport drive mechanism comprises a lead screw and a stepper motor.

25. The system as defined in claim 1, further comprising:

a door member for selectively controlling communication between the vacuum lock chamber and the sample receiving chamber of the mass spectrometer.

26. The system as defined in claim 25, further comprising:

a sample storage chamber for storing one or more of the plurality of sample supports; and

another door member for controlling communication between vacuum lock chamber and the sample storage chamber.

27. The system as defined in claim 1, further comprising:

a pump for selectively evacuating the vacuum lock chamber.

28. The system as defined in claim 1, wherein:

each of the plurality of sample supports is moveable between the vacuum lock chamber and the receiving chamber of the mass spectrometer; and

a transporter for moving one of the plurality of samples supports within the vacuum lock chamber while the plurality of samples on another of the sample supports are being struck with laser pulses.

29. The system as defined in claim 1, further comprising:

a powered sample support transporter for moving one or more of the plurality of sample supports within the vacuum lock chamber.

30. The system as defined in claim 1, further comprising:

a vent valve for selectively venting the vacuum lock chamber to atmospheric pressure.

31. The system as defined in claim 1, wherein the support transfer mechanism is responsive to the computer means.

32. The system as defined in claim 1, wherein the support transfer mechanism includes a fluid cylinder and an actuator rod extending between the fluid cylinder and a respective sample support.

33. The system as defined in claim 1, wherein:

each of the plurality of sample supports includes an electromagnet secured thereto; and

power to each electromagnet is controlled in response to the computing means.

34. The system as defined in claim 1, wherein the x-y mechanism is an x-y table responsive to the computer means.

35. The system as defined in claim 1, further comprising:

an electrically conductive block within the sample receiving chamber for receiving a respective sample support; and

one or more insulating members electrically insulating the powered positioning mechanism from the electrically conductive block.

36. The system as defined in claim 35, further comprising:

a securing mechanism for temporarily affixing the position of a respective sample support with respect to the electrically conductive block.

37. The system as defined in claim 1, further comprising:

an attenuator for adjusting the intensity of a laser beam output from the laser source.

38. The system as defined in claim 37, wherein the attenuator is responsive to the computer means.

39. The system as defined in claim 1, where the computer means interprets test data from the mass spectrometer.

40. A system for analyzing a plurality of samples, comprising:

a plurality of portable sample supports each having a sample receiving surface thereon for accommodating a plurality of samples each at a fixed location on each sample support;

sample identification means for identifying each sample location of each of the plurality of samples on each of the plurality of sample supports;

support identification means for identifying each of the plurality of sample supports; and

a mass spectrometer for analyzing each of the plurality of samples on a respective one of the sample supports, the mass spectrometer having a sample receiving chamber therein for receiving a respective sample support;

a laser source for striking each sample on each sample support while within the receiving chamber with a laser pulse to desorb and ionize sample molecules;

support transfer mechanism for automatically inputting and outputting each of the sample supports from the sample receiving chamber of the mass spectrometer;

a vacuum lock chamber connected with the sample receiving chamber of the mass spectrometer for receiving each of the sample supports and for maintaining one or more of the sample supports within a vacuum controlled environment while the plurality of samples on another of the sample supports are struck by laser pulses;

a sample storage chamber for storing one or more of the plurality of sample supports;

a powered transporter for transporting each of the plurality of sample supports from the sample storage chamber to the vacuum lock chamber; and

computer means for controlling the support transfer mechanism and for receiving information from the sample identification means and the support identification means for recording test data from the mass spectrometer for each of the plurality of samples on each of the sample supports.

41. The system as defined in claim 40 further comprising;

a sample loading mechanism for positioning each of a plurality of liquid samples on the sample receiving surface of each of the plurality of sample supports; and

a curing chamber for drying each of the plurality of liquid samples on each of the sample supports to form a plurality of solid samples each positioned on a respective sample support.

42. The system as defined in claim 40, further comprising:

a pump responsive to the computer means for pumping liquid samples to a respective one of the sample supports.

43. The system as defined in claim 40, wherein each of the plurality of portable sample supports comprises an electrically conductive sample plate having a plurality of predetermined sample positions on the sample receiving surface.

44. The system as defined in claim 40, wherein:

the sample identification means includes a marking on each sample support for identifying each of the plurality of samples on the sample receiving surface.

45. The system as defined in claim 40, wherein a sample support includes a magnetic handle for cooperating with the support transfer mechanism to position the sample support.

46. The system as defined in claim 40, wherein each of the plurality of sample supports includes a sample holder and a plurality of pins each removably positionable with respect to the sample holder, each of the plurality of pins having a sample receiving surface thereon for receiving a respective one of the plurality of samples.

47. The system as defined in claim 40, wherein each of the plurality of sample supports has one or more locating members for precisely positioning the sample support.

48. The system as defined in claim 40, wherein each of the sample supports comprises in excess of 80 determined sample positions on the sample receiving surface.

49. The system as defined in claim 40, wherein the powered transporter is automatically responsive to the computer means.

50. The system as defined in claim 40, further comprising:

a transport cassette for supporting a plurality of sample supports each a preselected position.

51. The system as defined in claim 50, further comprising:

a transport drive mechanism for selectively positioning the transport cassette within the storage chamber; and

the transport drive mechanism being powered in response to the computer means.

52. The system as defined in claim 40, further comprising:

a door member for selectively controlling communication between the vacuum lock chamber and the sample receiving chamber of the mass spectrometer.

53. The system as defined in claim 52, further comprising:

another door member for controlling communication between vacuum lock chamber and the sample storage chamber.

54. The system as defined in claim 40, further comprising:

a powered sample support transporter for moving one or more of the plurality of sample supports within the vacuum lock chamber.

55. The system as defined in claim 40, wherein the support transfer mechanism includes a fluid cylinder and an actuator rod extending between the fluid cylinder and a respective sample support.

56. The system as defined in claim 40, wherein:

each of the plurality of sample supports includes an electromagnet secured thereto; and

power to each electromagnet is controlled in response to the computing means.

57. The system as defined in claim 40, further comprising:

powered positioning mechanism for selectively positioning each of the plurality of sample supports within the sample receiving chamber.

58. The system as defined in claim 57, further comprising:

the powered positioning mechanism is an x-y table responsive to the computing means;

an electrically conductive block within the sample receiving chamber for receiving a respective sample support; and

one or more insulating members electrically insulating the powered positioning mechanism from the electrically conductive block.

59. The system as defined in claim 40, further comprising:

an attenuator responsive to the computer means for adjusting the intensity of a laser beam output from the laser source.

60. A method of analyzing a plurality of samples within a sample receiving chamber of a mass spectrometer, the method comprising:

supporting each of a plurality of samples at a fixed location on one of a plurality of sample supports;

identifying each sample location of each of the plurality of samples on each of the plurality of sample supports;

providing a vacuum lock chamber for receiving the sample supports and for maintaining one or more of the sample supports within a vacuum controlled environment while the plurality of samples on another of the sample supports are struck by laser pulses;

automatically inputting and outputting each of the sample supports from the sample receiving chamber of the mass spectrometer to the vacuum lock chamber;

moving each sample support within the sample receiving chamber in both an x direction and a y direction perpendicular to the x direction;

striking each sample on each sample support while within the receiving chamber with a laser pulse to desorb and ionize sample molecules; and

recording test data in a computer from the mass spectrometer for each of the plurality of samples on the sample support.

61. The method as defined in claim 60, further comprising;

positioning each of a plurality of liquid samples on the sample receiving surface of each of the plurality of sample supports; and

drying each of the plurality of liquid samples on each of the sample supports to form a plurality of solid samples each positioned on a respective sample support.

62. The method as defined in claim 61, further comprising:

automatically preparing each of the plurality of liquid samples for deposit on a respective sample support.

63. The method as defined in claim 60, further comprising:

arranging each of the plurality of samples in each sample support in a plurality of rows and in a plurality of columns.

64. The method as defined in claim 60, wherein the step of identifying includes:

marking each sample support for identifying each of the plurality of samples.

65. The method as defined in claim 60, further comprising:

forming in excess of 80 predetermined sample positions on each of the respective sample supports.

66. The method as defined in claim 60, further comprising:

storing one or more of the plurality of sample supports within a sample storage chamber; and

automatically transporting each of the plurality of sample supports from the sample storage chamber to the vacuum lock chamber in response to the computer.

67. The method as defined in claim 60, further comprising:

supporting each of the plurality of sample supports at a preselected position within a transport cassette.

68. The method as defined in claim 60, further comprising:

selectively positioning the transport cassette in response to the computer.

69. The method as defined in claim 60, further comprising:

controlling communication from within the vacuum lock chamber to the environment exterior of the vacuum lock chamber in response to the computer.

70. The method as defined in claim 60, further comprising:

moving a sample support with the vacuum lock chamber while the plurality of samples on another of the sample supports are being struck with laser pulses.

71. The method as defined in claim 60, further comprising:

controlling an x-y table in response to the computer for positioning the plurality of samples within the sample receiving chamber of the mass spectrometer.

72. The method as defined in claim 71, further comprising:

supporting each of the plurality of sample supports on an electrically conductive block within the sample receiving chamber; and

electrically insulating the x-y table from the electrically conductive block.

73. The method as defined in claim 72, further comprising:

temporarily affixing the position of a respective sample support with respect to the electrically conductive block.

74. The method as defined in claim 60, further comprising:

adjusting the intensity of a laser beam output from the laser source in response to the computer.

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